REGULATION OF THE CILIATED CELL PROGRAM IN AIRWAY PROGENITORS
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The goal of this project is to investigate mechanisms responsible for the emergence and diversification of airway epithelial cells in the respiratory system. Multiciliated cells are a crucial component of the airway epithelium, being responsible for ciliary transport in concert with water and ion transport for optimization of airway clearance, in addition to being unique sites for expression of drug transporters and growth factor receptors. Altered number, morphology or function of ciliated cells is associated with a variety of diseases, including asthma, chronic obstructive pulmonary disease (COPD) and ciliopathies, such as primary ciliary dyskinesia (PCD). Our preliminary studies implicate Notch as a critical signal for ciliated versus secretory cell fate selection during development; moreover, E2F4 has been shown to be essential to form multiciliated cells in the respiratory epithelium. Recently the Hippo-YAP pathway has emerged as a major regulator of cell growth and differentiation, being also implicated in ciliogenesis. Nevertheless, how Notch, E2F4 and Hippo-YAP influence the molecular and cellular events associated with differentiation of the airway epithelium and how multiciliated cells become distinct regionally or in response to injury, is unclear. We propose to address these questions using gain and loss function genetic models and a well-established primary airway epithelial culture system. Thus, in this project we propose to: 1) Investigate the cellular and molecular events associated with initiation of ciliated cell fate in the developing airways, looking at the role of E2F4 and Notch signaling ; 2) Study the role of Hippo-YAP in ciliogenesis by manipulating YAP expression or phosphorylation in vivo and in primary airway epithelial cultures; 3) Study mechanisms that modulate the ciliated cell phenotype in airway progenitors of the developing lung, focusing on the Notch pathway.